Chapter

Probiotics as Potential Antimicrobials for the Treatment of Infections: current Reality or Remote Future?

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Abstract

Probiotics are microorganisms that live in symbiosis with the human body. The intake of probiotics in adequate amounts can improve biological functions bringing improvements in the health of the host. Many studies have demonstrated the indisputable antimicrobial activity of probiotics and their potential for an alternative treatment of infections. Nevertheless, the forms of encapsulation, as well as clinical trials on the clinical use of these microorganisms as a recognized and well-established protocol, are still incipient. In this chapter, we provide a general approach to the topic and point to future directions in the probiotics field for this purpose. Moreover, microbial resistance is a current public health problem and the search for new therapeutic alternatives is urgent. Probiotics and other natural therapies have been considered very promising. The approaches of future research should focus mainly on the isolation of new probiotic microorganisms, the definition of inoculum, forms of encapsulation for controlled delivery, and clinical trials for the definition of doses and mechanism of action in the fight against infections.

Keywords: probiotics, pharmacology, antimicrobial activity, microbiota, biomaterials

1. Introduction

The human body is inhabited by numerous microorganisms, including bacteria, fungi, viruses, and protozoa, which represent the human microbiota. Compared to the number of human cells, there is a much larger number of microorganisms [1], which affect the host's physiological functions in different ways [2]. After a long time of science focusing on pathogenic microorganisms that cause human diseases, the interest was also turned to those that provide benefits to the organism, such as probiotics.

The first time that probiotics were mentioned and defined was in 1965 and the concept was restricted to substances produced by bacteria that promote the growth of other bacteria [3]. In 2001, the Food and Agriculture Organization of the United Nations (FAO) updated the concept of probiotics for any living microorganisms that provide health benefits to the host when ingested in adequate quantities [4]. The most widely used and studied probiotics for human health benefits are generally gram-positive bacteria that function primarily as modulators and maintainers of gut health [5]. Examples of widely studied probiotics such as *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Enterococcus*, *Bacillus e Streptococcus* [6].

The commensal intestinal microbiota is related to important functions for maintaining the health of the organism, such as increased resistance against infections, differentiation of the immune system, and synthesis of nutrients [7]. Nevertheless, recent studies have shown that the benefits of probiotics for human health go beyond [8], including anti-inflammatory activities [9], anti-tumor activities [10], antioxidant [11], antimicrobial [12] and modulation of the microbiome [13]. Although, research on the antimicrobial activity of probiotic microorganisms remains incipient and its clinical applicability for the treatment of infections has not been fully explored [14].

Infections have been commonly treated with antibiotics. However, the unrestrained and irrational use of these drugs can range from individual harms, such as specific adverse effects of the drug for the patient, to serious public health problems, such as the selection of drug-resistant microorganisms [15]. Likewise, research on alternative therapies for the treatment of infectious diseases should be encouraged and the field of probiotic microorganisms is very promising. Therefore, in this chapter, we will discuss the current reality of treating infections using probiotic microorganisms and/or their by-products as well as the prospects for this therapy to become a reality in current medicine.

2. Probiotic microorganisms

In 1965, Lilly and Stillwell first used the term probiotic, describing substances that one organism secretes and can stimulate the growth of another [16]. Nonetheless, its use goes back to millennia, as the use of recipes with fermented milk by Greeks and Romans. There are also reports of the use of sour milk in the bible. Thus, it is observed that the benefits of the use of probiotics to human health have been discussed for millennia [17].

These microorganisms, when colonizing the gastrointestinal tract, interact directly with the cells of the immune system, playing an important role in the maintenance and balance of the immune system [18]. The mechanisms of action of probiotics are complex and, in most cases, likely, more than one mechanism occurs simultaneously. The main biological pathways of action include increased epithelial barrier, inhibition of microbial adhesion and competitive exclusion of pathogenic microorganisms in addition to the production of antimicrobial substances, modulation of the immune system, maintenance of normal levels of short-chain fatty acids, and regulation of intestinal absorption of electrolytes [19].

The word "probiotic" comes from Greek and means "for life" [20]. Probiotics are viable live microorganisms, bacteria, and yeasts, which confer benefits to the health of the host when ingested in adequate concentration. Probiotic microorganisms, in general, are part of the intestinal microflora, but can also be found in ecological environments. Many factors need to be considered before isolating a potential probiotic microorganism. Initially, it is necessary that the strain is not pathogenic and shows some type of behavior that reflects in biological activities

Genus	Specie	Main source	Reference
Lactobacillus	*L. casei*, *L. bulgaricus*, *L. acidophilus*, *L. rhamnosus*, *L. reuteri*, *L. pantarum* and *L. johnsonii*	Dairy and human gastrointestinal tract	[26, 27]
Bifidobacterium	*B. animalis*, *B. bifidum*, *B. breve*, *B. infantis*, *B. lactis*, *B. longum*	Human, Dog, Primate, Pig, Cow and Horse gastrointestinal tract	[28–30]
Streptococcus	*Streptococcus thermophilus*	Dairy	[31, 32]
Enterococcus	*Enterococcus faecalis*, *Enterococcus faecium*	Human, Cow and Pig gastrointestinal tract	[33–35]
Pediococcus	*Pediococcus pentosaceus*, *Pediococcus acidilactici*	Dry quark and rice wine	[36]

Table 1.
Main probiotic microorganisms that are cited in the literature for human health benefits.

for the benefit of the host [21]. Besides, it is important to consider that the probiotic action is not universal for all species and does not work the same in all tissues of the body [22].

Lactic acid bacteria (*Lactococcus*, *Lactobacillus*, *Streptococcus*, and *Enterococcus*) are among the most well-known microorganisms, used and studied by man for probiotic purposes. In addition to these, we can include, *Bifidobacterium* and *Saccharomyces* species, a non-pathogenic yeast [23–25]. **Table 1** summarizes the main probiotic microorganisms mentioned in the literature for the benefit of human health.

Microorganisms can produce lactic acid from different carbon sources, as well as release secondary metabolites, including bacteriocins, exopolysaccharides, and enzyme complexes with antimicrobial properties preventing the installation and growth of other microorganisms [21, 37]. The mechanisms involved in the action of these microbial products are well understood concerning the benefits generated to the human intestine. However, the use of probiotics for alternative antimicrobial therapy against infections, in general, is incipient, although promising. Subsequently, we will discuss how probiotics can affect a human microbiota, ways of encapsulation, and their main uses for treating infections.

3. Probiotics affect the microbiota

In recent years, several findings have revealed benefits in the administration of probiotics, ranging from direct inhibition of pathogenic microorganisms to improvements in host immune system functions [38–43].

Despite a large number of studies with probiotics, most efforts are focused on understanding the benefits for the intestinal health of the host. Probiotics can exert their antimicrobial activity through different mechanisms of action. Generally, it has been reported that these microorganisms control/kill the pathogenic microbiota through the production of inhibitory substances such as bacteriocins and hydrogen peroxide (capable of inhibiting Gram-negative and Gram-positive pathogenic bacteria); interference at adhesion sites; competition for nutrients in the microenvironment, among others [41, 42, 44, 45]. Besides, there is also the modulation of the immune system, which also plays a role in the control of infections, which can occur in several ways: increased non-specific phagocytic activity through the activation of macrophages [9, 45, 46].

Several probiotic species are widely used in research showing its benefits to the host [46, 47]. Among these benefits, antimutagenic properties [48], anticarcinogenic properties [49–51], antidiarrheal drugs [52–54], system stimulation [55], prevention of atopic dermatitis [56–58], reduced blood cholesterol [59, 60].

Therefore, the use of probiotics has been considered a promising strategy for the prevention and control of various infectious diseases [38–40, 42, 43, 48, 61–63].

Some studies have also demonstrated the importance of probiotics relating to multidrug-resistant bacteria [64]. Multidrug-resistant bacteria, such as vancomycin resistant enterococcus (VRE), carbapenemase-producing enterobacteria (CPE), and extended-spectrum beta-lactamase (ESBL)-carrying strains, represent a major public health issue because they are potential pathogens associated with a high mortality rate [64, 65]. Prevention strategies could be based on the use of probiotics to prevent the colonization of the colon microbiota. Transient colonization with multidrug-resistant bacteria could result in the transfer of antibiotic resistance genes in commensals or potential pathogens, resulting in the persistence of the resistance gene in the microbiota, which could be responsible for an increased risk of lethal infection due to the delay in introducing an effective antibiotic [64, 66]. Surprisingly, clinical cases demonstrated that fecal transplantation was able to cause decolonization of microbiota of naturally resistant Extended Spectrum β-lactamase (ESBL) bacterial strains [67–69]. Furthermore, there are reports that the composition of the microbiota of hospitalized patients is related to the susceptibility to colonization with multiresistant bacteria. The use of probiotic microorganisms such as *L. plantarum* or *L. fermentum* reduced the colonization of resistant pathogens such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa* or *Candida albicans* [70, 71]. Nevertheless, an in vitro study showed that the culture supernatants of *Clostridium butyricum*, *C. difficile*, *Clostridium perfringens*, *Enterococcus faecium*, and *L. plantarum* were able to suppress the growth and transmission of gene resistance of bacteria carrying ESBL and Carbapenemase-Producing Enterobacteriaceae (CPE) [64]. It is undeniable that both colonization by probiotics and the use of their by-products have great potential in the treatment and prevention of infections, however these properties are still scarcely explored.

Vancomycin-resistant enterococci (VRE) seem less adapted to survival in the intestinal microbiota. Thus, these pathogens are more susceptible to decolonization when compared to other multiresistant bacteria. The intestinal microbiota in patients suffering from hematologic malignancies is less frequently colonized by VRE in the presence of *Barnesiella* [7]. In vivo evidence demonstrates that supplementing resident microbiota with *Barnesiella* or *Lactobacillus paracasei* CNCM I-3689 reduces VRE colonization in mice [72, 73]. In clinics, a case report showed VRE decolonization after fecal grafting for the treatment of *C. difficile colitis* [64].

The clinical use of probiotics in the treatment of infection is challenging the thinking of encapsulation for delivery. It is necessary to maintain the viability of these microorganisms long enough to compete with pathogenic microorganisms. Next, we'll discuss different potential encapsulation modalities for delivery.

4. Biomaterials for encapsulation of probiotics

The drug delivery systems through liposomes, micelles, carbon nanotubes, and dendrimers allowed the increase of therapeutic efficacy, reduction of toxicity, sustained and controlled release [74, 75]. The biotechnology industry has been aiming at the development of techniques for encapsulating probiotics, since their health benefits are indisputable. However, unlike inert substances, probiotics are live microorganisms, which in a way is a challenge in their manufacture, as they must be

kept in a live/viable state during the processing, storage, and gastrointestinal transit steps to ensure its effectiveness on target sites [75].

The encapsulation technique consists of a set of physical–chemical or mechanical processes in which solid, liquid or gaseous materials are packaged, trapped in another material, usually hydrocolloidal materials, resulting in the formation of particles that vary in shape and size (from nanometer to millimeter) [76–78].

The encapsulated part is named core material, internal phase, active agent, or payload phase, and the encapsulating agent is called the carrier, shell, external phase, or matrix [78]. From these components, the encapsulation forms different structures: reservoir (where the core is surrounded by a shell), matrix (the internal phase is distributed on the surface), or coated matrix, in which matrix is surrounded by an additional coating layer [78].

The use of nanoencapsulation techniques (<1 μm) is not feasible because of the size of the bacteria (1 to 5 μm) [76]. On the other hand, it is possible to obtain microcapsules using other techniques [79, 80]. The first microencapsulation techniques applied were spray drying, freeze-drying or lyophilization, foam drying, and fluidized bed drying [78]. Other techniques used are extrusion, emulsion technologies, gel particles, coacervation, and electrospraying [76, 78, 81].

The encapsulation of probiotics can be made using natural polymers, such as polysaccharides, polypeptides, and polynucleotides, or synthetic polymers. Conventionally, three processes are involved in encapsulation. First, the cells must be incorporated into a matrix, which can be liquid (by dissolution or dispersion) or solid (by agglomeration or adsorption). Then the solution must be dispersed (liquids) or sprayed (solids) on the surface. The last process aims to stabilize the structure, through polymerization, gelling, solidification, evaporation, coacervation, or coalescence [79].

Before choosing the technique, it is necessary to consider some important criteria: the relationship between the composition of the material, type of bacteria, temperature and pH of the medium, as well as the host's immune response. The biocompatibility of the material used in the encapsulation is directly related to the viability of the probiotics, which must remain equal to or greater than 107 CFU/ml [82, 83]. Therefore, factors such as solubility, digestibility, and release capacity must also be carefully analyzed [84]. Consequently, it is expected that the biomaterial will be able to form an effective protective barrier to resist pH variations and ensure the survival of bacteria, without causing damage to the host organism. Next, some biomaterials commonly used for the encapsulation of probiotics will be discussed.

4.1 Alginate

It is a natural polysaccharide composed of alginic acid (β-D-manuronic acid and L-gunoronic acid), obtained through some types of seaweed (laminaria). It is considered the most used material for the encapsulation of probiotics. Calcium alginate is preferable because it associates the biocompatibility of the material with a simple and low-cost technique. However, some disadvantages are attributed, such as the high porosity of the particles, which can reduce the protection of cells in the matrix [85] and sensitization in an acid medium [86]. Nonetheless, the association of alginate with other polymeric components or the addition of additives to the surface of the particles can easily overcome these defects [87]. Alginate spheres reach the intestine satisfactorily, without undergoing significant degradation by stomach acids [88]. Besides, the structural configuration of the probiotic encapsulation to alginate is comparable to the beneficial biofilm formation by probiotics bacteria [89].

4.2 Chitosan

It is a biodegradable copolymer obtained from the deacetylation of chitin (polysaccharide) present in the crustacean exoskeleton. It consists of units of D-glucosamine, capable of forming polymeric networks through Cross-link due to the presence of free amino groups. It is commonly found associated with another polymer since studies have shown that its isolated use in the matrix does not contribute to the maintenance of cell viability [86]. When applied in multilayers together with calcium alginate, have shown promising results, where the particles are coated with chitosan forming polyelectrolyte complexes that reinforce the alginate structure [89, 90]. Although its use is relatively common, care should be taken when choosing this biomaterial to encapsulate some types of bacteria, such as those from lactic acid, since chitosan can cause their inhibition [91]. Additionally, its solubility is directly related to the pH of the medium, being insoluble at pH higher than 5.5 [92], which may result in null or insufficient release.

4.3 Carrageenan

These natural polymers are extracted from red algae (Rhodophyceae) and are commonly used as additives in the food industry. Three variables are found: (kappa) k-carryenink, (iota) i-carrageenan and (lambda) λ-carrageenan [93]. The use for encapsulation of probiotics is based on the sol–gel transition characteristics of the types k-carrageenan and i-carrageenan [93]. The dissolution of the polymer occurs after heating in a temperature range between 40 and 45°C, at which point the bacteria must be incorporated. Subsequently, the solution is stored at room temperature allowing gelation to occur, forming a three-dimensional gel [87]. Studies have shown that bacteria have been kept viable, demonstrating a promising effect of the use of carrageenan [94–96].

4.4 Gellan gum

This polysaccharide comes from the bacterium *Sphingomonas elodea*. It is composed of glucose (60%), rhamnose (20%), and gluconic acid (20%). These microbial polysaccharides are considered water-soluble polymers and are commonly used as solidifying, gelling, or stabilizing agents [97]. Other microbial polysaccharides, such as arabic gum, jamilam, and xanthan gum, when associated with gelam gum, become very promising for the encapsulation of probiotics [98].

4.5 Cellulose acetate phthalate (CAP)

They are polysaccharides derived from plants that have important characteristics, such as insolubility at pH below 5 and solubility at pH above 6. Thus, it can be used effectively to enable encapsulated probiotics to reach the intestine and be released gradually without being altered by stomach pH [99]. CAP does not form a gel, therefore, it is used as a coating agent for other biomaterials.

4.6 Starches

Another polysaccharide extracted from plants. Resistance to degradation by pancreatic enzymes present in the small intestine is an interesting characteristic that justifies its use as a probiotic delivery agent, guaranteeing the viability of bacteria when reaching the large intestine [86, 100]. It is commonly associated with alginate or carrageenan to form resistant capsules or gels [87, 101].

4.7 Synthetic polymers

The use of synthetic material for encapsulating probiotics requires that it must be a biodegradable material and provide bacterial viability. An example of these polymers is PVA - poly (vinyl alcohol), characterized by being soluble in water, chemically stable, and of low cost. Studies have shown that its use the use of this material alone [102] or associated with other biomaterials [103] is satisfactory while maintaining the viability of probiotic microorganisms. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), poly(ethylene oxide) (PEO), and poly(vinyl pyrrolidone) (PVP) are other synthetic polymers used for encapsulation of probiotics synthetic polymers used for encapsulation of probiotics [84]. The use of these polymers is linked to the technique of producing fibers through electrospinning.

All of these alternatives mentioned aim to encapsulate probiotics for intestinal delivery. Although they can be applied to other tissues of the body, the data in the literature are incipient and need to be better analyzed for application in the treatment of other infections, such as those discussed in the next topic.

5. Prevention and treatment of infection with probiotics

The resistance of pathogenic microorganisms to synthetic antimicrobials and, consequently, the ineffectiveness of conventional therapies and recurrence of infections reflects the need to seek alternative and/or supplementary methods in the treatment protocols [104]. Probiotics are one of the methods and are considered promising, as they provide satisfactory results when facing infections of a bacterial, fungal and viral nature, whether in the intestinal, urinary, respiratory, female genital tracts, and in the oral cavity. In addition, it is safe and does not promote adverse effects on the human body [105, 106]. **Figure 1** schematizes the delivery of microencapsulated probiotic microorganisms in an epithelium colonized by pathogenic microorganisms for the treatment of an infection.

One indication of probiotics refers to the treatment of *Helicobacter pylori* infection, which is one of the most common chronic bacterial infections in humans, with approximately 4.4 billion infected individuals worldwide in 2015 [107]. *H. pylori* infection is associated with the development of gastric cancer, which represents one of the main global causes of cancer-related deaths [108, 109]. The treatment of *H. pylori* infection is based on its eradication, with the use of antibiotics, such as amoxicillin, clarithromycin, and metronidazole. However, antibiotic therapy promotes an imbalance in the intestinal microbiota and increased levels of resistant bacteria [110], as well as species associated with persistent gastric inflammation and gastric carcinogenesis [111]. This situation justifies probiotic supplementation, aiming to reduce undesirable changes in the intestinal microbiota, promote the eradication of *H. pylori* [108, 112], produce significant improvements in gastrointestinal symptoms, and, consequently, in the quality of life of individuals [108, 109]. The combination of probiotics with antibiotic therapy for the eradication of *H. pylori* was suggested in the Thailand Consensus, held in 2015 [110].

Probiotics, in addition to reducing the density of *H. pylori*, promote immune responses with reduced inflammatory status [112–115], significantly reduce adverse events related to antibiotic treatment, and improve patient compliance [109, 116]. Despite this evidence, it was highlighted in the Thailand Consensus, that most studies that evaluated the effects of probiotics on the eradication of *H. pylori* are of poor quality, compromising general recommendations. It has been suggested that

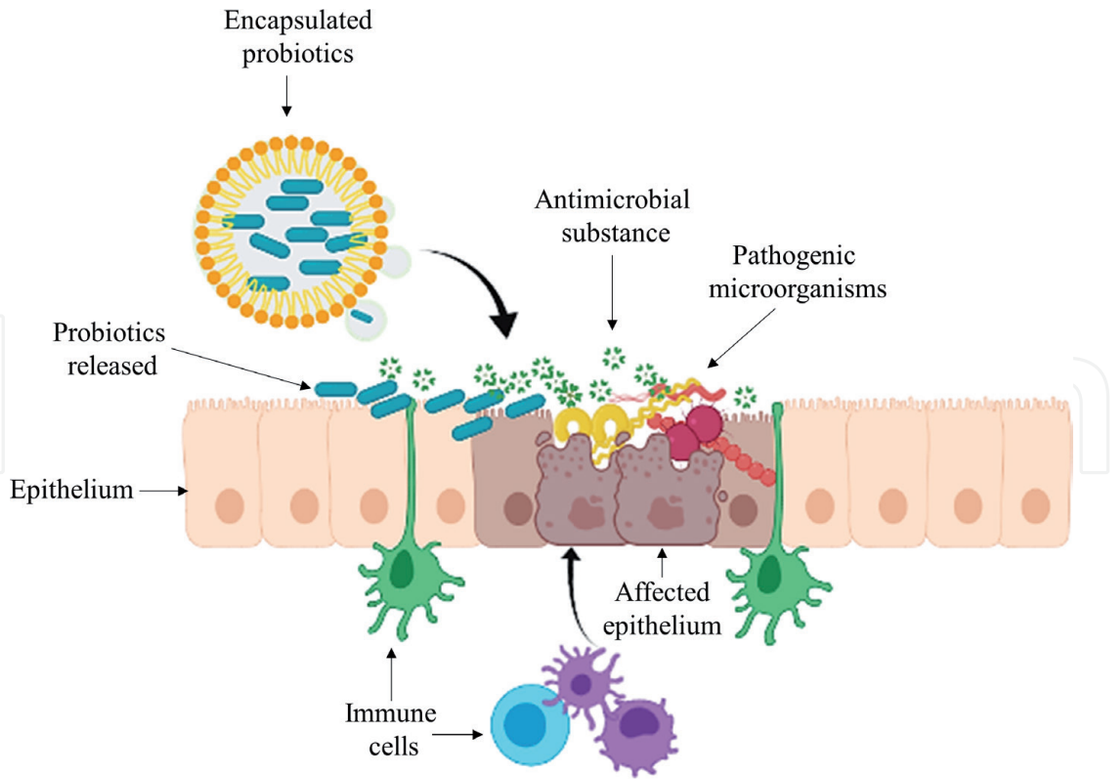

Figure 1.
Microencapsulated probiotics being delivered for the treatment of infection in epithelial tissue. Note that after the exit of the microorganisms from the micelle there is the colonization of the region and release of bacteriocins that in addition to acting as antimicrobials, stimulate the host's immune system.

further studies should be carried out to determine the best strain, the ideal dose, the duration of treatment, effectiveness, contraindications, and cost–benefit [110].

Probiotics are also indicated to reduce or prevent diarrhea associated with antibiotics and infections by *Clostridium difficile*, common in hospitalized patients [117, 118] and the elderly [119]. In children, its effectiveness in preventing antibiotic-associated diarrhea [120] and in treatment for acute gastroenteritis has not been confirmed, despite reducing the duration of hospitalization [121]. The use of probiotics in the treatment of infections by *Enterobacteriaceae* producing extended-spectrum β-lactamase has also been discussed. However, the results are incipient to indicate its use in eradication therapy in patients with prolonged intestinal transport of *Enterobacteriaceae* [122].

Some studies have suggested that supplementation with probiotics can improve the host's innate and acquired immune response, promoting a protective effect against respiratory infections [46, 123, 124]. The increase in the population of T cells, more precisely CD4 and CD8, is one of the most important mechanisms of the anti-infection effect of probiotics [125, 126]. Oral probiotics, when used in children, in addition to improving intestinal microecological balance can reduce the frequency of respiratory tract infections [89], mostly caused by viruses, such as the coronavirus [127], influenza [128], and bacteria, such as *Streptococcus pneumoniae*) [129]. Several studies have found that probiotics reduce episodes of acute respiratory tract infections in children, adults, the elderly, and athletes [89, 125, 126, 130, 131], proving its beneficial effect in these populations, with no reports of adverse effects in children [131].

The high recurrence of urinary tract infections in children [132] and the possibility of developing microbial resistance to drugs used against this disease have justified research with non-antibiotic alternatives, such as the use of probiotics for the prevention of recurrent urinary infections in this population

[133]. Probiotics appear to prevent recurrent urinary infections by contributing to the recovery and maintenance of microbiomes, by reducing the adherence, growth, and colonization of infectious pathogens in the urinary tract, in addition to improving host defenses, and attenuating or eliminating inflammation [105, 134–144]. Unlike the beneficial role of the use of probiotics in preventing urinary infections in children [132], it appears to have no protective effect in adults with severe spinal injuries, who have recurrent urinary infections [145], as well as in healthy young women [146].

Regarding the genital tract, the administration of probiotics, alone or as adjunctive therapy to the use of conventional antimicrobials, demonstrates success in the treatment of infections such as bacterial vaginosis and vulvovaginal candidiasis, common and recurrent infections in women of reproductive age. These infections that produce abnormal vaginal discharge, itching, vulvar odor, are associated with important health complications, such as the increased transmission of sexual infections, risk of premature birth, and pelvic inflammation, with negative impacts on quality of life [138, 147–149].

In infections that affect the mouth, candidiasis is also one of the most prevalent diseases, especially when local factors are predisposing the installation of the infection. Probiotics have been suggested for the treatment of oral candidiasis because they reduce the population of *Candida* ssp. [150], the course of treatment with conventional antifungal therapies [151], and the severity of clinical manifestations of the infection associated with prosthetic stomatitis [152, 153], including asymptomatic [62]. Besides, the immunological and antimicrobial potential of probiotics also can be used in the treatment of periodontal disease killing periodontopathogens, as Porphyromona gingivalis, and promoting the expression of some favorable immunoregulatory effects [154]. In summary, probiotics favor oral health, increasing fluids in the mucosa, reducing the accumulation of dental biofilm and gingival inflammation, improving the clinical signs characteristic of periodontal infection, such as redness and swelling [63, 155, 156].

Studies show beneficial effects of the combination of probiotics in the treatment regimen for different infections, with improvements in the clinical condition and patient adherence to treatment. Although, researchers warn of the need for further studies to define the best treatment protocol, including the determination of effects, contraindications, and cost–benefit [110].

6. Concluding remarks

Today's society is experiencing a public health problem related to an exponential increase in microbial resistance, compared to the slow evolution of new drug development. The human organism is attacked daily by countless pathogenic microorganisms, many of which cause lethal infections. The use of alternative therapies, alone or as an adjunct to antibiotics, is a reality. Concerning the use of probiotics, its effectiveness in modifying the microbial is unquestionable, either by the production of antimicrobial bacteriocins or by the modulation of the immune system. Nonetheless, there is no consensus or standardization for the clinical use of probiotics for the treatment of infectious diseases, except its use for the recomposition of the intestinal microbiota. Moreover, two important challenges need to be overcome: the standardization of carriers to deliver these microorganisms effectively to the treatment site and the definition of important factors, such as the mechanism of action, standardization of inoculum, and therapeutic protocols, based clinical trials. Thus, although promising, widespread antimicrobial therapy with probiotics is not yet a reality for clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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